REMARKS

Claims 1-5, 7-27 and 29-34 are currently pending in the above-identified application. Claims 1, 22 and 34 have been amended to recite an a reassortant rotavirus that comprises a gene which encodes a protein that is immunologically cross-reactive with an antigenically distinct human VP7 serotype in order to set forth the invention with greater particularity. Support for this amendment can be found, for example, in page 9, lines 15-17, and throughout the specification. No new matter has been added by these amendments. Applicants respectfully request reconsideration of the claims in the present application in light of the above amendments, the attached declaration of Dr. Albert Kapikian and the remarks below.

Claim Rejections Under 35 USC §112

Claims 5 and 15 remain rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. As previously stated, Applicants will provide a Declaration assuring the public availability of the deposited material when allowed claims have been agreed upon, should the claim language agreed upon require such a declaration.

Claim Rejections Under 35 USC §103

Claims 1-4, 7-14, and 16-21 remain rejected under 35 U.S.C. §103(a) as being unpatentable over Midthun *et al.* (*J. Virol.* 1985; 53:949-954), designated Midthun '85, Midthun *et al.* (*J. Clin. Microbiol.* 1986; 24:822-826), designated Midthun '86, Hoshino *et al.* (*J. Med. Virol.* 1997; 51:319-325), and Clark *et al.* (US 6,113,910). As stated in the prior office actions and restated in the pending office action the Examiner believes that Clark *et al.* teach a general range of suitable administrative dosages and that the range of disclosed doses is indicative of conventional routine optimization used in the vaccine art for each individual administration. The

Examiner believes that "[t]he prior art clearly teaches different dose ranges for optimal results for each rotavirus vaccine composition comprising various structural and functional features" citing *In re Aller* (105 USPQ 233, 235 (CCPA1955)) for the proposition that "[w]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."

Applicants must again respectfully disagree with the Examiner's summary and analysis of the art of record and the motivation and expectations asserted for the skilled artisan. As stated in Applicants' prior response the Examiner has alleged that the artisan of ordinary skill would have been motivated to optimize the dosage for each patient to reduce detrimental side effects and that a reasonable expectation existed that the compositions of the present invention would not only be immunogenic, but that the compositions would be effective and not possess any detrimental effects. Contrary to the position of the Examiner one of skill in the art would not have been motivated to use a dosage of any bovine rotavirus vaccine at a dosage of less than 10^6 pfu, much less a human x bovine UK reassortant rotavirus. Further, Applicants do not believe that the skilled artisan would have had a reasonable expectation that a dosage of human rotavirus x bovine UK reassortant rotavirus of less than 10^6 would induce an effective immunogenic response in a human vaccinee.

Applicants in a prior response summarized the disclosure of studies using various prior bovine rotavirus and human x bovine rotavirus reassortants. The results of the prior clinical studies demonstrated that none of the compositions had been successful initiating an effective immune response when used at a dosage below 10^7 pfu much less 10^6 pfu. The Examiner has considered these remarks and asserted that "[t]he different dose ranges provided for each of the rotavirus compositions are due to structurally distinct features and activities of each reassortant rotavirus" and the art teaches that the skilled artisan need only optimize to find the proper dose. Applicants believe this reasoning is completely contrary to *In re Aller* cited by the Examiner.

In *Aller* the process claimed by the appellants was identical to a chemical process was disclosed in the prior art, except for the use of different temperatures and acid concentrations. The reactants therefore had the same structural and functional features and all that was altered were certain reaction conditions. In the present case the process of clinical testing, administration to a human subject, is the same as that used in the art, but the structural and functional features of the compositions tested are different than the compositions tested in the prior art. It is these structural and functional features of the human x bovine UK reassortant rotavirus that determine whether they will be safe, immunogenic and protective in a human. Therefore, the "general conditions" of the claims are not disclosed in the prior art and Applicants are not merely optimizing workable ranges by routine experimentation.

Further, the cited art teaches that others had failed to obtain an effective immunogenic composition with bovine rotavirus strains other than bovine rotavirus UK when the virus was used at a concentration of less than about 10^7 pfu. Therefore, as above Applicants do not believe that the compositions and methods of the present invention are merely indicative of conventional routine optimization used in the vaccine art as asserted by the Examiner. In particular, one of skill in the art would not have expected compositions comprising such a low amount of a bovine rotavirus would possess sufficient immunogenicity to be effective. There is no evidence in the prior art suggesting to the skilled artisan that a composition comprising less than 10^6 pfu of a human x bovine reassortant based on the bovine UK strain would provide an effective immunogenic composition.

The Examiner has also combined the Midthun *et al.* references with the teachings of Clark and Hoshino and concluded that the reference provide a reasonable expectation of protective efficacy with a multiple rotavirus reassortant vaccine composition. In particular, the Examiner believes that Hoshino *et al.* teaches that the 4 human serotypes present in the reassortants of the Midthun *et al.* references are the most epidemiologically important. In addition to the teachings of Hoshino, the Examiner believes that the teachings of the Midthun

references of neutralization of the rotavirus constructs with monoclonal antibodies to each VP7 human glycoprotein and the disclosure of Clark *et al.* of a vaccine composition comprising multiple rotavirus reassortants provide a more than reasonable expectation of success for combining the rotavirus reassortants of either Midthun *et al.* reference into an efficacious vaccine composition.

As stated previously by Applicants the combination of the Midthun *et al.* references with Hoshino *et al.* and Clark do not provide motivation to one of skill in the art to pursue compositions comprising less than $10^{6.0}$ pfu of each human x bovine UK rotavirus reassortant. The references also do not provide a reasonable expectation of success for combining any human x bovine UK reassortant rotavirus at any concentration to produce an efficacious vaccine composition.

The Midthun *et al.* references as noted by the Examiner describe the selection of human x bovine UK rotavirus reassortants by neutralization of the recombined human x bovine rotavirus constructs with monoclonal antibodies to each VP7 human glycoprotein. But, this process is a selection of a rotavirus reassortant having the desired VP7 antigen using hyperimmunized guinea pig antiserum specific for bovine VP7. The disclosed process for selecting the desired VP7 serotype reassortant has no predictive value as to the effective immunogenicity of the rotavirus reassortant when administered to an individual. Further, Midthun *et al.* disclose the characterization of the selected human x bovine UK reassortant rotavirus with hyperimmunized guinea pig antiserum specific for each human VP7 serotype. As with the selection process, the characterization of the reassortant rotavirus with hyperimmunized guinea pig antiserum has no predictive value as to the effective immunogenicity of the rotavirus reassortant when administered to an individual. See paragraph 3 of the Kapikian declaration attached.

Hoshino *et al.* while disclosing four clinically important serotypes of rotavirus, adds nothing to the expectation of whether human x bovine UK reassortants used individually or

in combination would be safe, immunogenic or effective at any concentration. As provided in the Kapikian declaration in paragraph 4, Hoshino *et al.* merely state that the reassortant vaccines should theoretically provide antigenic coverage for the four disclosed strains, but that safety, immunogenicity and protective efficacy of the individual components as well as combination would need to be tested in humans. The testing would require administration to adults and small children for safety and immunogenicity and administration to infants and young children for protective efficacy in the target population.

Clark *et al.* disclose "a vaccine composition comprising multiple rotavirus reassortants," but the reassortants are based on the bovine WC3 bovine rotavirus strain and its derivatives. Also, the Examiner has asserted that Clark provides a suitable dosage range supporting the notion that it was the difference structural and functional features of the various rotavirus that required the range of dosages and that the methods were known for testing each dosage. As above the compositions of Clark were only found to be protectively effective at concentrations of greater than 10^7 pfu. These disclosures therefore do nothing to provide the skilled artisan with any expectation regarding the use any human bovine UK reassortant rotavirus composition at a dosage of less than 10^6 pfu as an effective immunogen. Clark and the other prior disclosures relating to bovine and human x bovine rotavirus reassortant vaccine compositions based on bovine rotavirus other than the bovine UK require dosages 10 to 100 times the dosages of the compositions disclosed in the present application that provide an immunogenically effective composition. It is well known in the art that the safety, immunogenicity and protective effectiveness of any rotavirus composition can only be tested empirically by testing in humans. See paragraphs 5 and 6 of the Kapikian declaration. Therefore, the prior disclosures do not disclose or suggest the present invention, but would in fact teach away from the compositions and methods claimed in the present application.

Based on the above amendments and remarks and the attached Kapikian declaration the Examiner is respectfully requested to reconsider and withdraw the rejection of

claims 1-4, 7-14 and 16-21 under 35 U.S.C. § 103(a) as unpatentable over Midthun *et al.* (*J. Virol.* 1985; 53:949-954), designated Midthun '85, Midthun *et al.* (*J. Clin. Microbiol.* 1986; 24:822-826), designated Midthun '86, Hoshino *et al.* (*J. Med. Virol.* 1997; 51:319-325), and Clark *et al.* (US 6,113,910).

Claims 22-34 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over Hoshino *et al.* (*J. Med. Virol.* 51:319-325, 1997) and Clark *et al.* (US 6,113,910) for the reasons of record for claims 22-33. The Examiner has also included claim 34 in this rejection because the claim encompasses the limitations of claims 22-33. In part, the Examiner has summarized the claims to encompass a method of stimulating the immune system to produce an effective immune response to a human VP7 rotavirus antigen serotype where each of the reassortants are administered at a dosage of less than $10^{6.0}$ pfu and that may be a combined composition. The compositions are also summarized as including the administration of an unlimited number of multiple administrations and as such can include hyperimmunization. Further, the Examiner states that Applicants have not disputed that guinea pigs are an acceptable model in the art with respect to human vaccine efficacy.

Applicants again must strongly disagree with the analysis of the Examiner. Applicants do not believe that the teachings of the reference are not directed to an art-recognized animal model of vaccine efficacy. Hoshino *et al.* teach the construction of certain human bovine rotavirus reassortants. These reassortants were administered individually to guinea pigs to produce hyperimmunized animals. In administering the reassortant rotavirus to the animals the antigen is provided in an amount and at a frequency that is intended to produce an immune response to both highly immunogenic and weakly immunogenic antigens in the rotavirus preparation. The guinea pig model is particularly useful for the study of the study of the mammalian immune response to rotavirus antigens because guinea pigs do not appear to undergo natural rotavirus infection. In fact, to date after 24 years of using the guinea pig model Applicants have not detected any antibodies to rotaviruses in hundreds of guinea pigs used. See

paragraph 7 of the Kapikian declaration. As the guinea pig does not acquire a natural rotavirus infection the antibodies produced are only specific to the rotavirus injected. But, because the guinea pig is not infected by the rotavirus it is not possible to extrapolate the immunogenicity data produced in the guinea pig to determine the immunogenicity of any composition in a human regardless of the antigen used. Therefore, the studies reported by Hoshino *et al.* can not characterize the safety or protective efficacy in humans. In addition, the authors draw no conclusions from the guinea pig data as to the possible immunogenicity of the compositions and instead indicate evaluation of the safety, immunogenicity and protective efficacy of the compositions would be carried out later. See Hoshino *et al.*, page 323, right column, lines 31-35.

The Examiner has also cited column 12, lines 29-31 and 40-45 of Clark as demonstrating that the guinea pig is an acceptable model in the rotavirus vaccine art for evaluating safety or protective efficacy in humans. Contrary to the assertion of the Examiner, the passages from Clark cited describe a method that includes the injection of guinea pigs intraperitoneally with a sample of virus in it host cell (WI78-1,6-11 in CV-1 cells). The injected animals are then observed for 15 days post-inoculation. This assay is not a test designed for evaluating safety or protective efficacy, but instead is an assay that appears to have been intended to monitor the sterility of the vaccine composition prior to administration to humans. See paragraph 8 of the Kapikian declaration. Therefore, the passage cited does not support the use of the guinea pig to evaluate safety or protective efficacy of a potential vaccine candidate in a human.

Applicants respectfully request the Examiner reconsider and withdraw the rejection of claims 22-34 under 35 U.S.C. § 103(a) as being unpatentable over Hoshino *et al.* and Clark *et al.* in view of the above amendments and remarks and the declaration of Dr. Kapikian.

CONCLUSION

Applicants respectfully request reexamination and reconsideration of the pending claims. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-467-9600.

Respectfully submitted,

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